Predicting cell of origin from digitized images of hematoxylin and eosin-stained slides of diffuse large B-cell lymphomas using a cell-based deep-learning model

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Introduction

- Diffuse large B-cell lymphoma (DLBCL) can be classified by cell of origin (COO) as an activated B-cell-like (ABC) or germinal center B-cell-like (GCB) tumor.[1]
- ABC and GCB tumors carry differing prognoses; patients with ABC tumors generally have a higher risk of poor treatment outcomes than those with GCB tumors.[2–4] Timely and accurate classification and risk stratification is therefore important for appropriate diagnosis and patient care, as well as the future design of COO-based clinical trials.
- Existing methods for determining COO, such as immunohistochemistry, can be time-consuming, weakly reproducible among pathology labs, and may poorly reflect the underlying tumor biology.[4,5] In addition, there is a lack of consensus on the preferred algorithms for COO prediction using immunohistochemistry.[6]
- With the aim of overcoming these challenges, we developed two deep learning (DL) models to classify DLBCL by COO using routinely stained hematoxylin and eosin (H&E) whole-slide images (WSIs). One model used tile-level features and the other used nucleus-based morphology.

Objective

- To develop and compare the performance of tile-level and nucleus-based DL models to perform COO classification using WSIs of H&E-stained pathology slides from patients with DLBCL.

Methods

- Algorithms were trained, validated and tested using data from the phase 2 CAVALLI (ClinicalTrials.gov identifier: NCT02055820) and phase 3 GOYA (ClinicalTrials.gov identifier: NCT01287741) trials.[7,8]
- The slides from GOYA were split into a training set and a test set for model tuning. The CAVALLI slides were used as an independent holdout set for further validation of the final model to prevent overfitting (**Table 1**).

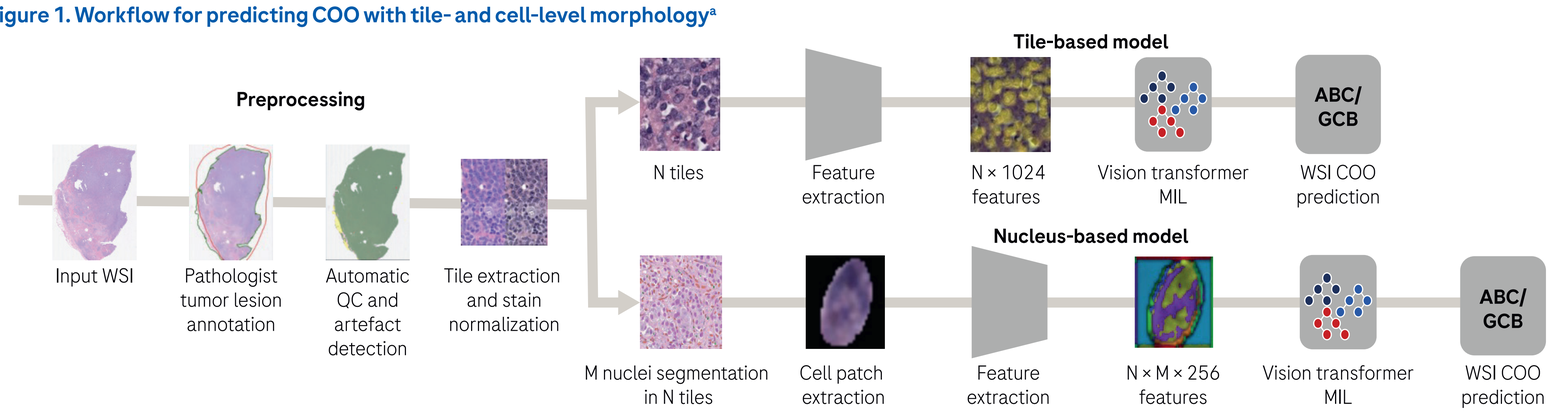
Table 1. Clinical trial data sets used to train, validate and test the DL models

Trial	ABC slides	GCB slides	Total slides	Set
Phase 3 GOYA[a]	106	202	308	Training
Phase 3 GOYA[a]	21	46	67	Test
Phase 2 CAVALLI[b]	57	110	167	Holdout

[a]ClinicalTrials.gov identifier: NCT01287741. [b]ClinicalTrials.gov identifier: NCT02055820.
ABC, activated B-cell-like; DL, deep learning; GCB, germinal center B-cell-like.

- Gene expression profiling was used to confirm the ground truth COO classification.
- Following preprocessing, features were extracted using a custom fixed network pretrained on digital pathology images using the ResNet-50 neural network and the self-supervised Bootstrap Your Own Latent (BYOL) method. A multiple instance learning transformer was used to aggregate extracted features and predict the WSI label in a weakly supervised manner (**Figure 1**).
  - Multiple instance and weakly supervised learning allow models to be developed using samples labeled at slide level, rather than requiring complete annotation of individual tiles, features and nuclei.
  - For the tile-based model, 1024 features per tile were extracted from tumor regions of the WSIs.
  - For the nucleus-based model, 256 features per nucleus were extracted from automatically segmented nuclei from the same tiles.
- For the analysis of quantifiable pathology features, tiles were clustered by unsupervised k-means clustering (k = 16). Clusters were split into ABC- or GCB-significant groups according to the proportion of ground truth ABC and GCB slides, and quantifiable pathology features were then analyzed for each cluster. Average quantifiable pathology features were also calculated per slide and ABC- and GCB-labeled slides were compared using Student's t-test.
- An explainability model was applied, which assigned attention gradients to individual cells to reflect how strongly each cell influenced GCB or ABC classification. Morphological characteristics of cells that had been assigned positive (GCB) or negative (ABC) attention gradients were then inspected by a pathologist to determine the features that influenced COO classification.

Figure 1. Workflow for predicting COO with tile- and cell-level morphology[a]

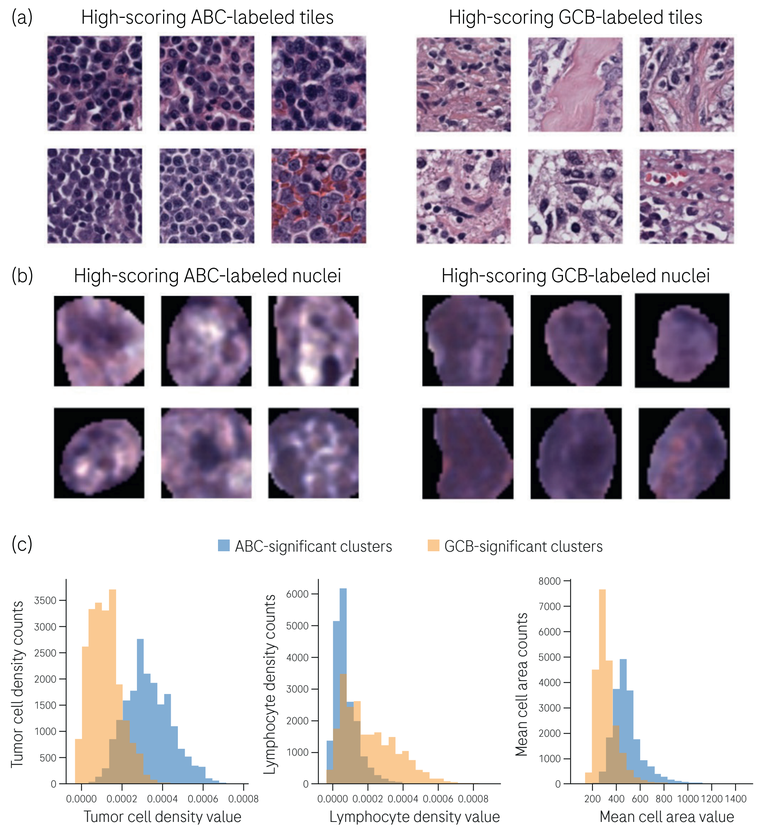


[a]The COO prediction models are investigational devices currently in development.
ABC, activated B-cell-like; BYOL, Bootstrap Your Own Latent; COO, cell of origin; GCB, germinal center B-cell-like; MIL, multiple instance learning; QC, quality control; WSI, whole-slide image.

Results

- Using the tile-based model, the areas under the receiver operating characteristic curves (AUCs) for the test set and holdout set were 0.73 and 0.67, and the average F1 scores were 0.68 and 0.61, respectively (**Table 2**).
- For the nucleus-based model, the AUCs for the test set and holdout set were 0.63 and 0.70, and the average F1 scores were 0.61 and 0.64, respectively (**Table 2**).
- On visual inspection of the highest-scoring tiles and nucleus patches, ABC-labeled tiles had higher tumor cell density than GCB-labeled tiles (**Figure 2a**) and ABC-labeled nuclei were larger than GCB-labeled nuclei (**Figure 2b**).

Figure 2. Morphological features associated with ABC- or GCB-labeled WSIs



ABC, activated B-cell-like; GCB, germinal center B-cell-like; WSI, whole-slide image.

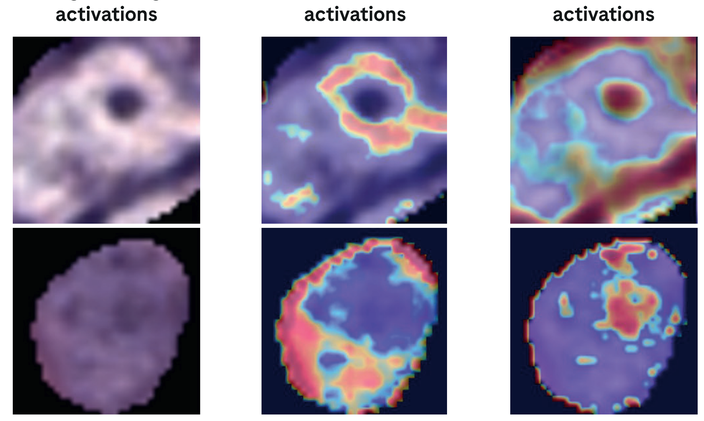
- For quantifiable pathology features, ABC-significant clusters had a higher tumor cell density, lower lymphocyte density and higher mean cell area than GCB-significant clusters (**Figure 2c**). The ratio of tumor to nontumor cells and the average tumor cell size were significantly higher for ABC-labeled slides (both $p < 0.001$).
- Inspection of the explainability model attention gradients and nucleus images revealed that more ABC classifications than GCB classifications were related to bright areas of nuclei with lower chromatin content (**Figure 3**).

Table 2. Performance of the DL models

Model type	Test set[a] (21 ABC slides, 46 GCB slides)		Holdout set[b] (57 ABC slides, 110 GCB slides)	
	AUC	Average F1 score	AUC	Average F1 score
Tile-based model	0.73	0.68	0.67	0.61
Nucleus-based model	0.63	0.61	0.70	0.64

[a]Phase 3 GOYA study. [b]Phase 2 CAVALLI study.
ABC, activated B-cell-like; AUC, area under the receiver operating characteristic curve; DL, deep learning; GCB, germinal center B-cell-like.

Figure 3. Explainability model attention gradients associated with ABC and GCB labeling



ABC, activated B-cell-like; GCB, germinal center B-cell-like.

Conclusions

- **These DL models demonstrated reasonable performance in COO classification of DLBCL from H&E-stained WSIs, without the use of ancillary techniques.**
- **The explainability model identified novel cellular and morphological features, including cell size and tumor cell density, that were associated with ABC or GCB classification.**
- **Following further validation and regulatory approval, these models have the potential to supplement the diagnostic toolkit available to pathologists for reliable COO classification in the future.**

References

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